Pembrolizumab Versus Placebo as Adjuvant Therapy in Resected Stage IIB or IIC Melanoma: Final Analysis of Distant Metastasis-Free Survival in the Phase III KEYNOTE-716 Study

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ABSTRACT

Clinical trials frequently include multiple end points that mature at different times. The initial report, typically based on the primary end point, may be published when key planned co-primary or secondary analyses are not yet available. Clinical Trial Updates provide an opportunity to disseminate additional results from studies, published in JCO or elsewhere, for which the primary end point has already been reported.

Pembrolizumab adjuvant therapy was shown to significantly improve recurrence-free survival (RFS) and distant metastasis-free survival (DMFS) in patients with resected stage IIB or IIC melanoma in earlier analyses of the randomized, double-blind, phase III KEYNOTE-716 study (ClinicalTrials.gov identifier: NCT03553836). We report results of the protocol-specified final analysis of DMFS for KEYNOTE-716. Overall, 976 patients were randomly allocated to pembrolizumab (n = 487) or placebo (n = 489). As of January 4, 2023, median follow-up was 39.4 months (range, 26.0-51.4 months). The median DMFS was not reached in either treatment group, and the estimated 36-month DMFS was 84.4% for pembrolizumab and 74.7% for placebo (hazard ratio [HR], 0.59 [95% CI, 0.44 to 0.79]). The median RFS was not reached in either treatment group, and the estimated 36-month RFS was 76.2% for pembrolizumab and 63.4% for placebo (HR, 0.62 [95% CI, 0.49 to 0.79]). DMFS and RFS results were consistent across most prespecified subgroups, including stage IIB and stage IIC melanoma. The safety profile of pembrolizumab was manageable and consistent with previous reports. These results continue to support the use of pembrolizumab adjuvant therapy in patients with resected stage IIB or IIC melanoma.

ACCOMPANYING CONTENT

Appendix

Protocol

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INTRODUCTION

In the randomized, double-blind, phase III KEYNOTE-716 study in patients with resected stage IIB or IIC melanoma, pembrolizumab as adjuvant therapy significantly improved recurrence-free survival (RFS) at the first interim analysis (hazard ratio [HR], 0.65 [95% CI, 0.46 to 0.92]; $P = .0066$)[1] and distant metastasis-free survival (DMFS) at the third interim analysis (HR, 0.64 [95% CI, 0.47 to 0.88]; $P = .0029$)[2] compared with placebo. These results led to the approval of pembrolizumab as adjuvant therapy in adult and pediatric patients with stage IIB or IIC melanoma by numerous regulatory authorities, including the US Food and Drug Administration and European Medicines Agency.[3,4] We report findings from the protocol-specified fourth interim analysis of KEYNOTE-716, including final DMFS and updated RFS results.

METHODS

Study Design and Patients

The design of KEYNOTE-716 (ClinicalTrials.gov identifier: NCT03553836) has been described previously.[1] Eligible patients were age 12 years and older with newly diagnosed, resected, histologically confirmed, stage IIB (T3b or T4a) or IIC (T4b) cutaneous melanoma without regional lymph node involvement confirmed pathologically by sentinel lymph node biopsy, as defined by the American Joint Committee on Cancer 2017 classification, 8th edition. Patients were required to have an Eastern Cooperative Oncology Group performance status (ECOG PS) of 0 or 1 and no previous treatment for melanoma beyond complete resection. Patients were randomly assigned in a 1:1 ratio to pembrolizumab 200 mg

TABLE 1. Baseline Demographics and Clinical Characteristics of the Intention-to-Treat Population

Characteristic	Pembrolizumab (n = 487)	Placebo (n = 489)
Age, years, median (range)	60 (16-84)	61 (17-87)
<65	303 (62.2)	295 (60.3)
≥65	184 (37.8)	194 (39.7)
Sex		
Male	300 (61.6)	289 (59.1)
Female	187 (38.4)	200 (40.9)
Race		
White	435 (89.3)	439 (89.8)
Other	10 (2.1)	5 (1.0)
Missing	42 (8.6)	45 (9.2)
ECOG status		
0	454 (93.2)	452 (92.4)
1	32 (6.6)	35 (7.2)
2	0	1 (0.2)
Missing	1 (0.2)	1 (0.2)
Geographic region		
United States	95 (19.5)	80 (16.4)
Not United States	392 (80.5)	409 (83.6)
T stage[a]		
T3a	2 (0.4)	0
T3b	200 (41.1)	201 (41.1)
T4a	113 (23.2)	116 (23.7)
T4b	172 (35.3)	172 (35.2)
Disease stage[a]		
IIA	1 (0.2)	0
IIB	309 (63.4)	316 (64.6)
IIC	171 (35.1)	169 (34.6)
IIIC	4 (0.8)	1 (0.2)
IV	0	2 (0.4)
Missing	2 (0.4)	1 (0.2)

NOTE. Data are No. (%) unless otherwise specified.
Abbreviations: ECOG, Eastern Cooperative Oncology Group; T, tumor.
[a]Patients not meeting inclusion criteria after random assignment were recorded as protocol deviations; however, these patients were still included in the intention-to-treat population.

(2 mg/kg up to 200 mg in pediatric patients) or placebo intravenously once every 3 weeks for 17 cycles or until disease recurrence, unacceptable toxicity, or withdrawal of consent. Randomization was stratified by T category (T3b, T4a, or T4b) for adults, with a separate stratum for patients age 12-17 years. The protocol and all amendments were approved by the appropriate institutional review board or ethics committee at each institution. All patients provided written informed consent.

End Points and Statistical Analysis

This fourth interim analysis was based on a target of 195 DMFS events. The primary end point was investigator-assessed RFS. Secondary end points included investigator-assessed DMFS and safety and tolerability. Efficacy was assessed in all randomly allocated patients (intention-to-treat [ITT] population). Safety was assessed in all patients who received ≥1 dose of study treatment. RFS and DMFS were estimated using the Kaplan-Meier method. A stratified Cox proportional hazards model with the Efron method of handling ties was used to assess the magnitude of treatment difference between groups, with HRs and 95% CIs with treatment as a covariate. There was no formal hypothesis testing because statistical significance criteria for RFS and DMFS were met at previous analyses. Prespecified subgroups included T category (T3b *v* T4a *v* T4b), age (<65 *v* ≥65 years), sex (male *v* female), race (White *v* non-White), ECOG PS (0 *v* 1), and geographic region (United States *v* non–United States). Post hoc analysis of RFS and DMFS by disease stage was also conducted. HRs and 95% CIs for subgroups were estimated using an unstratified Cox proportional hazards model.

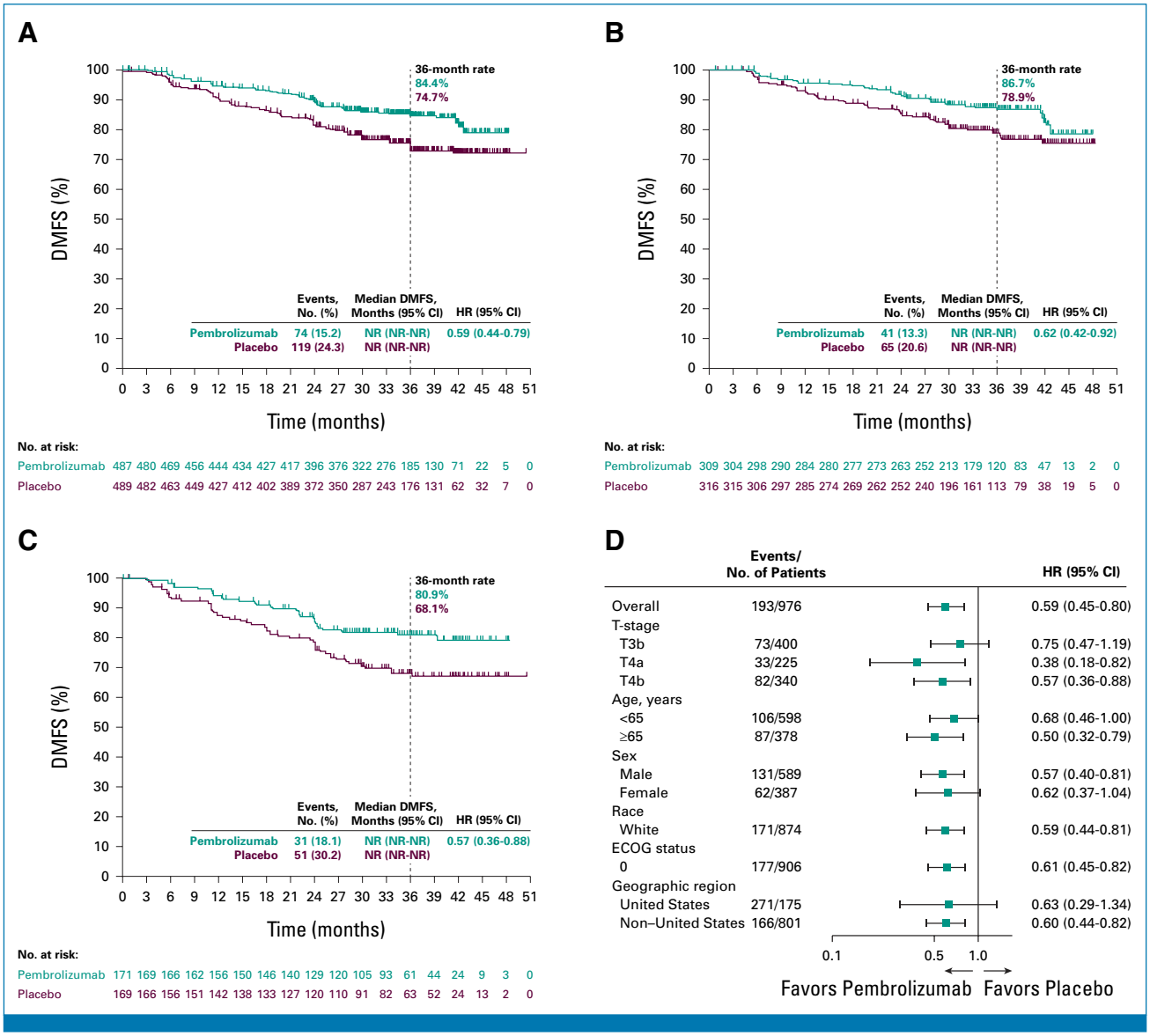

FIG 1. Kaplan-Meier estimates of DMFS (A) in the ITT population, (B) in patients with stage IIB melanoma, and (C) in patients with stage IIC melanoma. (D) Forest plot of key subgroups. DMFS, distant metastasis-free survival; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; ITT, intention-to-treat; NR, not reached; T, tumor.

RESULTS

Patients

A total of 976 patients were randomly allocated to pembrolizumab (n = 487) or placebo (n = 489). Baseline characteristics were generally balanced between treatment groups (Table 1). The median time from random assignment to data cutoff (January 4, 2023) was 39.4 months (range, 26.0-51.4).

Efficacy

The median DMFS in the ITT population was not reached (NR) in either group (HR, 0.59 [95% CI, 0.44 to 0.79]; Fig 1A). The estimated 36-month DMFS rate was 84.4% for pembrolizumab and 74.7% for placebo. In patients with stage IIB disease, the median DMFS was NR in both groups and the 36-month DMFS rate was 86.7% for pembrolizumab and 78.9% for placebo (HR, 0.62 [95% CI, 0.42 to 0.92]; Fig 1B). In patients with stage IIC disease, the median DMFS was NR in both groups and the 36-month DMFS rate was 80.9% for pembrolizumab and 68.1% for placebo groups, respectively (HR, 0.57 [95% CI, 0.36 to 0.88]; Fig 1C). DMFS across prespecified subgroups is shown in Figure 1D.

The median RFS in the ITT population was NR in both groups (Fig 2A). The estimated 36-month RFS rate was 76.2% for pembrolizumab and 63.4% for placebo (HR, 0.62 [95% CI, 0.49 to 0.79]). In patients with stage IIB disease, the median

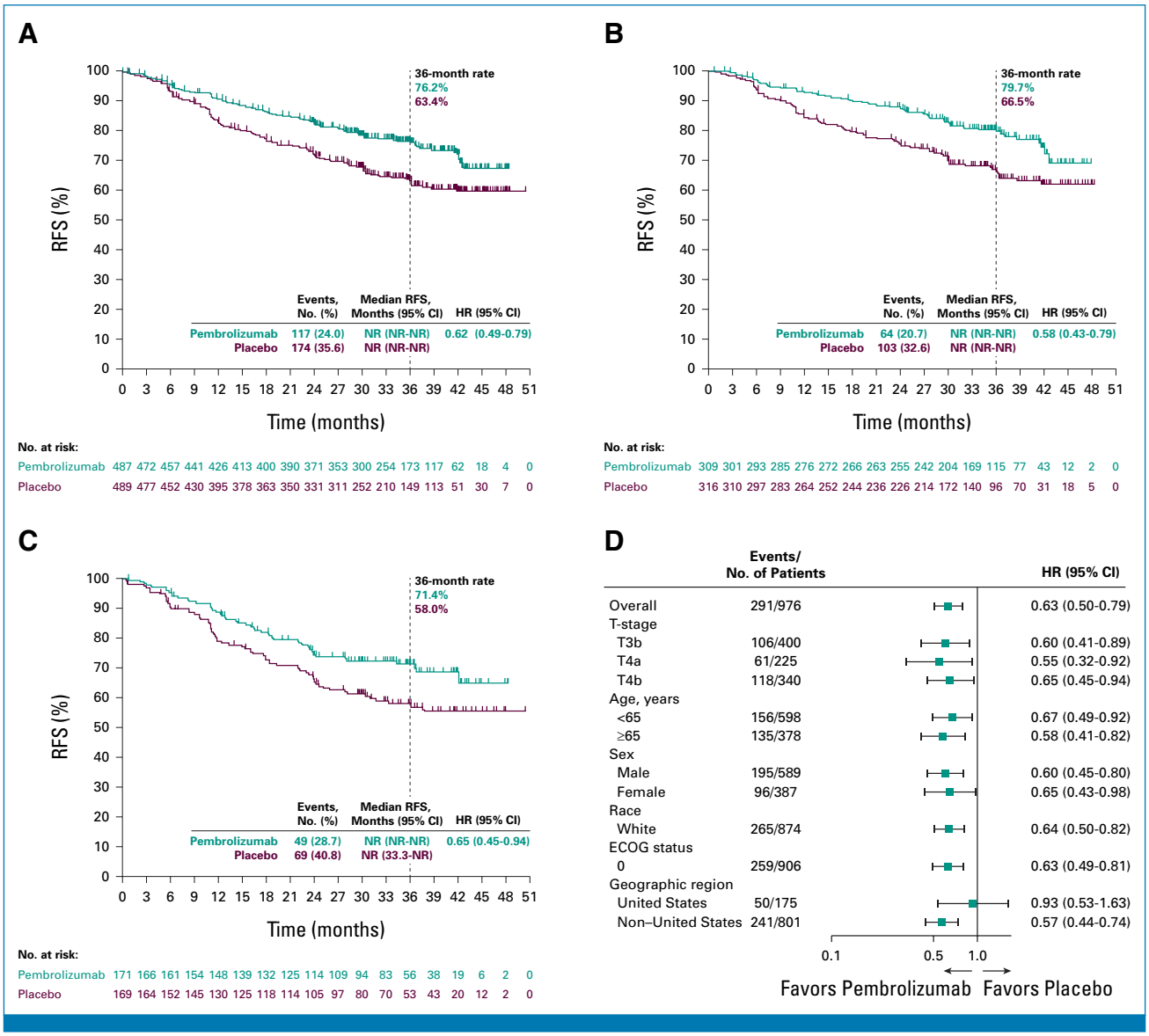

FIG 2. Kaplan-Meier estimates of RFS (A) in the ITT population, (B) in patients with stage IIB melanoma, and (C) in patients with stage IIC melanoma, and (D) RFS in key subgroups. ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; ITT, intention-to-treat; NR, not reached; RFS, recurrence-free survival; T, tumor.

RFS was NR in both groups and the 36-month RFS rate was 79.7% for pembrolizumab and 66.5% for placebo (HR, 0.58 [95% CI, 0.43 to 0.79]; Fig 2B). In patients with stage IIC disease, the median RFS was NR in both groups and the 36-month RFS rate was 71.4% for pembrolizumab and 58.0% for placebo (HR, 0.65 [95% CI, 0.45 to 0.94]; Fig 2C). RFS across prespecified subgroups is shown in Figure 2D.

Safety

Overall, 483 patients in the pembrolizumab group and 486 in the placebo group received ≥1 dose of study treatment. Treatment-related adverse events (TRAEs) occurred in 82.6% of patients in the pembrolizumab group (grade 3/4, 17.2%) and 63.6% in the placebo group (grade 3/4, 5.1%; Appendix Table A1, online only). TRAEs led to treatment discontinuation in 15.9% and 2.5% of patients in the pembrolizumab and placebo groups, respectively. No patients died because of TRAEs. Immune-mediated AEs and infusion reactions occurred in 37.9% of patients in the pembrolizumab group (grade 3/4, 11.0%) and 9.5% in the placebo group (grade 3/4, 1.2%; Appendix Table A2).

DISCUSSION

In this protocol-specified fourth interim and final DMFS analysis of KEYNOTE-716, pembrolizumab adjuvant therapy continued to demonstrate a DMFS and an RFS benefit

compared with placebo in patients with resected stage IIB or IIC melanoma. After an additional 12 months of follow-up, the DMFS benefit previously reported at the third interim analysis was sustained,[2] with pembrolizumab providing a reduction in the risk of distant metastasis compared with placebo. The DMFS benefit was also consistent across prespecified subgroups, including stage IIB and IIC melanoma. The RFS benefit previously observed with pembrolizumab was also sustained, with pembrolizumab reducing the risk of recurrence or death in the ITT population, in patients with stage IIB or stage IIC melanoma, and in most subgroups.[1,2] The HRs for DMFS and RFS in the current analysis were also consistent with previous reports, indicating that the benefit observed with pembrolizumab is durable.[1,2] For both DMFS and RFS, a continued separation of the Kaplan-Meier curves was observed over time and appeared to be widening for DMFS. The safety results also support previous studies showing pembrolizumab has a manageable safety profile.[1,2,5] Overall survival results will be reported at the fifth interim analysis.

Patients with stage IIB and IIC melanoma have a similar prognosis as that for patients with stage III melanoma and have a similar or greater risk of recurrence than patients with stage IIIA and stage IIIB melanoma.[6-8] Pembrolizumab is the first systemic adjuvant therapy to be approved for use in patients with stage II melanoma, and, to our knowledge, KEYNOTE-716 is the only study with long-term follow-up data available. Other studies investigating adjuvant treatments include the phase III CheckMate-76K study. In a prespecified interim analysis of patients with resected stage IIB or IIC melanoma enrolled in CheckMate-76K, adjuvant nivolumab improved RFS (HR, 0.42 [95% CI, 0.30 to 0.59]; $P < .0001$) and DMFS (HR, 0.47 [95% CI, 0.30 to 0.72]) compared with placebo, which confirmed the benefit of adjuvant therapy with an anti–PD-1 agent in the population.[9] Additional studies underway include the phase III COLOMBUS-AD study, which is being conducted to investigate adjuvant encorafenib plus binimetinib versus placebo in resected stage IIB or IIC *BRAF*^{V600}-mutated melanoma.[10] Adjuvant pembrolizumab treatment for patients with resected high-risk stage IIB-IV melanoma is also being investigated as coformulation with vibostolimab in the phase III KEYVIBE-010 study[11] and in combination with the individualized neoantigen therapy V940 in the phase III V940-001 study.

In the final DMFS analysis of KEYNOTE-716, pembrolizumab continued to demonstrate manageable safety and a clinically meaningful DMFS and RFS benefit compared with placebo, supporting the use of pembrolizumab adjuvant therapy in patients with resected stage IIB or IIC melanoma.

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APPENDIX

TABLE A1. TRAEs in the As-Treated Population

	Pembrolizumab (n = 483)		Placebo (n = 486)	
TRAE With Incidence ≥5%	Any Grade, No. (%)	Grade 3-4,[a] No. (%)	Any Grade, No. (%)	Grade 3-4,[a] No. (%)
Any	399 (82.6)	83 (17.2)	309 (63.6)	25 (5.1)
Pruritus	119 (24.6)	3 (0.6)	52 (10.7)	0 (0.0)
Fatigue	104 (21.5)	1 (0.2)	93 (19.1)	1 (0.2)
Diarrhea	90 (18.6)	5 (1.0)	56 (11.5)	1 (0.2)
Arthralgia	79 (16.4)	1 (0.2)	39 (8.0)	0 (0.0)
Rash	78 (16.1)	7 (1.4)	34 (7.0)	1 (0.2)
Hypothyroidism	77 (15.9)	0 (0.0)	13 (2.7)	0 (0.0)
Hyperthyroidism	49 (10.1)	1 (0.2)	3 (0.6)	0 (0.0)
Asthenia	47 (9.7)	1 (0.2)	40 (8.2)	0 (0.0)
ALT level increased	39 (8.1)	4 (0.8)	22 (4.5)	1 (0.2)
Nausea	37 (7.7)	0 (0.0)	33 (6.8)	0 (0.0)
Rash maculopapular	36 (7.5)	2 (0.4)	9 (1.9)	0 (0.0)
Myalgia	32 (6.6)	2 (0.4)	16 (3.3)	0 (0.0)
AST level increased	31 (6.4)	1 (0.2)	11 (2.3)	1 (0.2)

Abbreviation: TRAE, treatment-related adverse event.
[a]There were no grade 5 TRAEs.

TABLE A2. Immune-Mediated Adverse Events and Infusion Reactions

	Pembrolizumab (n = 483)		Placebo (n = 486)	
Event	Any Grade, No. (%)	Grade 3-4,[a] No. (%)	Any Grade, No. (%)	Grade 3-4,[a] No. (%)
Any	183 (37.9)	53 (11)	46 (9.5)	6 (1.2)
Adrenal insufficiency	13 (2.7)	5 (1.0)	0 (0.0)	0 (0.0)
Arthritis	2 (0.4)	1 (0.2)	2 (0.4)	0 (0.0)
Colitis	20 (4.1)	8 (1.7)	5 (1.0)	0 (0.0)
Hepatitis	11 (2.3)	9 (1.9)	3 (0.6)	2 (0.4)
Hyperthyroidism	51 (10.6)	1 (0.2)	3 (0.6)	0 (0.0)
Hypophysitis	12 (2.5)	3 (0.6)	0 (0.0)	0 (0.0)
Hypothyroidism	83 (17.2)	0 (0.0)	18 (3.7)	0 (0.0)
Infusion reactions	3 (0.6)	0 (0.0)	7 (1.4)	0 (0.0)
Myasthenic syndrome	2 (0.4)	2 (0.4)	0 (0.0)	0 (0.0)
Myelitis	1 (0.2)	1 (0.2)	0 (0.0)	0 (0.0)
Myocarditis	1 (0.2)	0 (0.0)	1 (0.2)	1 (0.2)
Myositis	6 (1.2)	3 (0.6)	1 (0.2)	0 (0.0)
Nephritis	7 (1.4)	3 (0.6)	0 (0.0)	0 (0.0)
Pancreatitis	2 (0.4)	2 (0.4)	0 (0.0)	0 (0.0)
Sarcoidosis	5 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)
Severe skin reactions[b]	15 (3.1)	14 (2.9)	3 (0.6)	3 (0.6)
Thyroiditis	8 (1.7)	0 (0.0)	2 (0.4)	0 (0.0)
Type 1 diabetes mellitus	2 (0.4)	2 (0.4)	0 (0.0)	0 (0.0)
Uveitis	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)

[a]There were no grade 5 immune-mediated adverse events.
[b]Includes bullous dermatitis, erythema multiforme, pemphigoid, pruritus, rash, maculopapular rash, pruritic rash, and pustular rash.